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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,381	05/16/2005	Douglas Wade Beight	X16014	3880

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ELI LILLY & COMPANY
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EXAMINER

RAHMANI, NILOOFAR

ART UNIT	PAPER NUMBER
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1625

NOTIFICATION DATE	DELIVERY MODE
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06/11/2007

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary

Application No.

10/535,381

Applicant(s)

BEIGHT ET AL.

Examiner

Niloofer Rahmani

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 May 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,9 and 11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,9 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6,9, and 11 are pending in the instant application and claims 7-8, and 10 are cancelled.

Priority

2. This application is filed on 05/16/2005, which is a 371 of PCT/US03/35969, filed on 11/24/2003, which claims benefit of 60/429982, filed on 11/27/2002.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6,9, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6,9, and 11 are rejected because inconsistent use of punctuation, specifically “,” and “;”. For example, in claims 1, line 6, applicants used “,”. In claim 1, line 19, applicants used “;”. Correction is required.

4. Claim 9 is rejected because the claims are self-conflicting. Pharmaceutical composition by definition must be effective yet non-toxic. Claim 9 is pharmaceutical composition without dosage limitation i.e. included both ineffective and toxic amount. It is recommended that “therapeutically effective amount” be incorporated in the claims.

5. ***Claim Rejections - 35 USC § 112***

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims.
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,

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8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to a method of treating cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1.

The state of the prior art: Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks

the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed

invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

Amount of guidance/working examples: On pages 108-113 (Table I) of the specification, applicant has examples of test compounds for inhibition assay of TGF-B Type I receptor kinase. However, applicant has not guidance or examples for treating cancer.

The breadth of the claims: The breadth of claims is drawn to a method of treating cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1.

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating cancer, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claim 11, for treating cancer, have been enabled by the instant specification.

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6. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3,9 and 11 are rejected under 103(a) as being unpatentable over Sawyer et al. of WO 2002094833.

Determination of the scope and content of the prior art (MPEP §2141.01)

Sawyer et al. teaches analog compounds, pharmaceutical composition and utility in claims 1-13 nearly identical to the instant claims 1-3,9, and 11.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims 1-3,9, and 11 and the reference claims 1-13 is that the reference claims have R₂ substituent being quinoline instead of isoquinoline in the instant application.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

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One having ordinary skill in the art would be motivated to modify the compounds of the reference to obtain the instant compounds because Quinoline and Isoquinoline are positional isomers. Therefore, one skill ordinary in the art can substitute one instead of the other. Also note compounds in claim 1 of reference, which only differ from the instant compounds in having a different positional isomer for N as the instant application. Compounds, which differ only in the placement of substituents in a ring system, is not absent unexpected results. *In re Jones*, 162 F.2d 638, 74 USPQ 152 (CCPA 1947).

7. Claim Rejections - Obvious Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 168 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130 (b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 9 and 11 are provisionally rejected under the judicially created doctrine obviousness-type double patenting as being unpatentable over the claims 1-4 of the Beight et al., US 2006/0040983. Although the conflicting claims

are not identical, they are not patentably distinct from each other because the current invention embraces the invention claimed in the above patent.

Determination of the scope and content of the prior art (MPEP §2141.01)

Beight et al. claimed analogs compounds, pharmaceutical composition and utility in claims 1-4 as the instant claims 1-3,9, and 11.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims 1-3,9, and 11 and the reference claims 1-4 is that the reference claims has R₂ substituent being quinoline instead of isoquinoline in the instant application.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

Quinoline and Isoquinoline are positional isomer. Therefore, one skill ordinary in the art can substitute one instead of the other. Also note compounds in claim 1 of reference, which only differ from the instant compounds in having a different positional isomer for N as the instant application. Compounds, which differ only in the placement of substituents in a ring system, is not absent unexpected results. *In re Jones*, 162 F.2d 638, 74 USPQ 152 (CCPA 1947).

This is provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been issued.

8. Claims 1-3,9 and 11 are provisionally rejected under the judicially created doctrine obviousness-type double patenting as being unpatentable over the claims 4-7 of the Sawyer et al., US 2006/0079680. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current invention embraces the invention claimed in the above patent.

Determination of the scope and content of the prior art (MPEP §2141.01)

Sawyer et al. claimed analogs compounds, pharmaceutical composition and utility in claims 4-7 as the instant claims 1-3,9, and 11.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims 1-3,9, and 11 and the reference claims 4-7 is that the reference claims has R₂ substituent being quinoline instead of isoquinoline in the instant application.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

Quinoline and Isoquinoline are positional isomer. Therefore, one skill ordinary in the art can substitute one instead of the other. Also note compounds in claim 4 of reference, which only differ from the instant compounds in having a different positional isomer for N as the instant application. Compounds, which differ only in the placement of substituents in a ring system, is not absent unexpected results. *In re Jones*, 162 F.2d 638, 74 USPQ 152 (CCPA 1947).

This is provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been issued.

9. Claims 1-3,9 and 11 are provisionally rejected under the judicially created doctrine obviousness-type double patenting as being unpatentable over the claims 1-7 of the Sawyer et al., US 7,087,626. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current invention embraces the invention claimed in the above patent.

Determination of the scope and content of the prior art (MPEP §2141.01)

Sawyer et al. claimed analogs compounds, pharmaceutical composition and utility in claims 1-7 as the instant claims 1-3,9, and 11.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims 1-3,9, and 11 and the reference claims 1-7 is that the reference claims has R₂ substituent being quinoline instead of isoquinoline in the instant application.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

Quinoline and Isoquinoline are positional isomer. Therefore, one skill ordinary in the art can substitute one instead of the other. Also note compounds in claim 1 of reference, which only differ from the instant compounds in having a different positional isomer for N as the instant application. Compounds, which differ only in the placement of substituents in a ring system, is not absent unexpected results. *In re Jones*, 162 F.2d 638, 74 USPQ 152 (CCPA 1947).

This is provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been issued.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas Mckenzie, can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information

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for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI

06/05/2007

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MARGARET SEAMAN

PRIMARY EXAMINER

GROUP 1625